IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/596,920
Applicants	:	Ties VAN BOMMEL et al.
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Title: ULTRASOUND CONTRAST AGENTS FOR MOLECULAR IMAGING

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer dated 15 September 2010, Applicants hereby respectfully submits this Reply Brief.

REMARKS

At the outset, Applicants reiterate and restate all of the arguments presented in the Appeal Brief filed on 20 July 2010. In response to the "Response to Argument" section of the Examiner's Answer, Applicants submit the following further Remarks.

The Rejections of Claims 15-29 and 32-33 over Hainfeld I & West

Claim 15

Among other things, the method of claim 15 includes receiving ultrasound sound wave reflections produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections from solid metal nano-particles

having an acoustic impedance above $35x10^5$ g/cm^{2}s.

Applicants respectfully submit that neither Hainfeld I nor West nor any combination thereof teaches or suggests receiving ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above 35.10^5 g/cm^{2}s produced by an ultrasonic wave in an animal or human subject.

The Examiner argues that "*it is clear from Hainfeld that the metal nanoparticles may be used for diagnostic imaging, including ultrasound.*"

Applicants respectfully disagree.

Applicants respectfully submit that Hainfeld I does not fairly teach, enable, or suggest to one skilled in the art that there is any likelihood of successful ultrasound sound wave diagnosis or imaging by receiving ultrasound sound wave reflections from solid metal nano-particles in an animal or human subject.

Hainfeld I consistently discusses the use of their nanoparticles in conjunction with electromagnetic radiation, and more specifically X-rays (see, e.g., all of the drawings in Hainfeld I). Hainfeld I discusses the properties of their nanoparticles which recommend them for X-ray imaging, namely: (1) **Hounsfeld Units (HU's)** which define the amount of X-ray attenuation of a voxel of an X-ray image from a material (see, e.g., col. 4, lines 19-50; col. 11, lines 64 – col. 12, line 13; col. 12, lines 50-52; col. 14, lines 25-27 & 37-42; col. 15, lines 4-5, etc.); and (2) their "**physical x-ray absorptive properties**" (see, e.g., col. 6, lines 47-53; col. 7, lines 8-64; Table 2).

In contrast, successful ultrasound sound wave diagnosis and imaging requires that the contrast agent provide sufficient reflection enhancement for the ultrasound sound waves (see, e.g., the present specification at page 2, line 1). This in turn depends upon the size of the particles and their **acoustic impedance** (see, e.g., the present specification at page 4, line 31 – page 5, line 11). The present specification includes a substantial discussion of these properties, and presents theoretical and experimental results in FIGs. 2-5.

Hainfeld I is devoid of any mention of the acoustic properties of their nanoparticles. Hainfeld I is devoid of any teachings, analysis, or data that would suggest that their nanoparticles would be suitable for ultrasound sound wave diagnosis and imaging.

Furthermore, there is nothing to suggest that there is any correlation between the X-ray absorption properties that Hainfeld I promotes for X-ray imaging, and the acoustic impedance properties desired for ultrasound sound wave diagnosis or imaging. Indeed, Hainfeld I discloses in column 9 several materials such as Bismuth and Lead that are recommended for their X-ray imaging method, but which have low acoustic impedances below 35 x 10^5 g/cm^{2}s (e.g., Bismuth = 21.5 x 10^5 g/cm^{2}s; Lead = 24.6 x 10^5 g/cm^{2}s) and therefore are not suitable for the method of claim 15 of this patent application.

Other than a **single word** that is incorrectly included among a laundry list of electromagnetic probes (for all one knows, it was simply added in by a patent attorney who drafted the patent application just to "cover all bases"), Hainfeld I makes absolutely no mention of anything to do with ultrasound sound waves. Applicants respectively submit that this single word cannot provide an enabling disclosure of ultrasound sound wave diagnosis or imaging by receiving ultrasound sound wave reflections from solid metal nano-particles, any more than if someone had filed a patent application with **nothing** but a four line specification that said merely:

> "*Various forms of electromagnetic radiation including x-rays, visible light, lasers, ultrasound, infrared, microwaves, radio frequencies, UV radiation, and other electromagnetic radiation at various frequencies may be employed to detect solid gold nanoparticles*"

and then tried to obtain allowance of claims from the USPTO for a method of ultrasound sound wave diagnosis or imaging by receiving ultrasound sound wave reflections from solid metal nano-particles. Indeed, that single, off-handed and incorrect, mention of "ultrasound" hardly constitutes an enabling disclosure any more than a simple statement that "any form or radiation of any kind may be used with any sort of particles of any material having any size or shape for imaging purposes."

Meanwhile, West does not remedy the deficiencies of Hainfeld I.

At the outset, like Hainfeld I, West fails to disclose ultrasonic sound wave

diagnosis or imaging by receiving ultrasound sound wave reflections from solid metal nano-particles. It most certainly does not disclose this in the cited paragraph 27 and claim 33.

Indeed, to the contrary, West very clearly and explicitly teaches away from using solid metal nano-particles in imaging. See, e.g., paragraph [0010]. Accordingly, West teaches that one should employ "*nanoparticles comprising one non-conducting or semiconducting core layer and at least one conducting shell layer.*" See, e.g., paragraph [0017]; paragraph [0021], lines 4-8; paragraph [0023]; paragraph [0025] lines 4-11; paragraph [0021], lines 4-8, paragraph [0021], lines 4-8.

Furthermore, West teaches methods of localized heating of nanoshells and imaging based on such heated nanoshells (e.g., near-IR imaging – see, e.g., paragraph [0062]). Toward this end, West employs a number of radiation sources, including ultrasound, to **heat** its nanoshells, and this heat is then detected with near-IR imaging. So, West discloses, for example in claims 12, 15, 33 and 34, that the radiation source for **heating** the nanoshells may include ultrasound, but West **does not disclose that that the imaging is performed from ultrasound sound wave reflections** from the nanoshells (**as opposed to infrared reflections** from the heated nanoshells, which West does disclose and claim).

So West does not teach or suggest that one should modify Hainfeld I's X-ray system to employ solid metal nano-particles having an acoustic impedance above $35x10^5$ g/cm^{2}s in an ultrasound sound wave diagnosis or imaging method which employs ultrasound sound wave reflections from the solid metal nano-particles.

Therefore, for at least these reasons, Applicants respectfully submit that claim 15 is patentable over Hainfeld I and West. Accordingly, Applicants respectfully request that the rejection of claim 15 over Hainfeld I and West be withdrawn.

Claim 16

Among other things, the method of claim 16 includes receiving ultrasound sound wave reflections produced by an ultrasonic wave in a sample or organ, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above $35x10^5$ g/cm^{2}s.

For similar reasons to those set forth above with respect to claim 15,

Applicants respectfully submit that no combination of the teachings of Hainfeld I and West would produce a method including this combination of features.

Therefore, for at least these reasons, Applicants respectfully submit that claim 16 is patentable over Hainfeld I and West. Accordingly, Applicants respectfully request that the rejection of claim 16 over Hainfeld I and West be withdrawn.

Claims 17-29, 32 and 33

Claims 17-29, 32 and 33 depend variously from claims 15 and 16 and are deemed patentable over Hainfeld I and West for at least the reasons set forth above with respect to claims 15 and 16.

The Rejections of Claims 15-23, 25-28 and 32-33 over Bekeredjian

Claim 15

Among other things, the method of claim 15 includes receiving ultrasound sound wave reflections produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above $35x10^5$ g/cm^{2}s.

Applicants respectfully submit that Bekeredjian does not disclose or suggest receiving ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above $35x10^5$ g/cm^{2}s.

The Examiner argues that "*the instant claim language is readable upon contrast agents comprising both (solid) gold nanoparticles and protinaceous microtubules*."

At the outset, it is noteworthy that the Examiner places the claim-word "**solid**" in parentheses, as the Examiner has not cited anything in Bekeredjian that actually discloses solid metal nano-particles. It is also unknown on what basis the Examiner believes it would have been obvious to have modified Bekeredjian's teachings to employ solid metal nano-particles.

Furthermore, even assuming *arguendo* that the Examiner's statement was true, Bekeredjian does not disclose "*contrast agents comprising both (solid) gold nanoparticles and protinaceous microtubules*." Instead, Bekeredjian discloses **attaching** gold colloids to the walls of microtubules, and administering the colloidal

gold-**bound** microtubules as the contrast agent. Gold-bound microtubules are not solid metal nanoparticles. Accordingly, it is evident that any sound wave reflections received by Bekeredjian would be received from these colloidal gold-bound microtubules, and not from solid metal nano-particles as recited in claim 15. Indeed, as disclosed in the present specification, the intensity of ultrasound sound wave reflections from such colloidal gold-bound microtubules are generally reduced compared to the solid metal nanoparticles claimed here (see, e.g., page 2, lines 21-25).

Therefore, for at least these reasons, Applicants respectfully submit that claim 15 is patentable over Bekeredjian. Accordingly, Applicants respectfully request that the rejection of claim 15 over Bekeredjian be withdrawn

Claim 16

Among other things, the method of claim 16 includes receiving ultrasound sound wave reflections produced by an ultrasonic wave in a sample or organ, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above 35.10^5 g/cm^{2}s.

For similar reasons to those set forth above with respect to claim 15, Applicants respectfully submit that claim 16 is patentable over Bekeredjian. Accordingly, Applicants respectfully request that the rejection of claim 16 over Bekeredjian be withdrawn.

Claims 17-23, 25-18, 32 and 33

Claims 17-23, 25-28, 32 and 33 depend variously from claims 15 and 16 and are deemed patentable over Bekeredjian for at least the reasons set forth above with respect to claims 15 and 16.

The Rejections of Claims 15-33 over Hainfeld I, West & Hainfeld II

With the exception of claims 30-31, the Examiner raises no new arguments regarding the rejections based on Hainfeld I, West & Hainfeld II. Accordingly, with the exception of claims 30 and 31, Applicants stand on the arguments presented in the Appeal Brief.

Claims 30 and 31

Among other things, the methods of claims 30 and 31 each include receiving ultrasound sound wave from solid rhenium nano-particles having an acoustic impedance above $35x10^5$ g/cm^{2}s.

The Examiner argues that "*Hainfeld II teaches that rhenium and other metal nanoparticles are capable of interaction with various energy sources, including ultrasound.*"

Claims 30 and 31 do not broadly and generally claim "*capable of interaction with.*"

Instead, claims 30 and 31 claim **receiving ultrasound sound wave reflections** produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections **from solid rhenium nano-particles** having an acoustic impedance above $35x10^5$ g/cm^{2}s.

Applicants respectfully submit that Hainfeld II does not teach or suggest the use of solid rhenium nano-particles in **ultrasound sound wave diagnosis or imaging**. Instead, Hainfeld II only teaches the use of nano-particles made from rhenium and a bunch of other materials suitable for a **therapeutic application to enhance energy delivery** to target tissue, for example via Compton scattering, the photoelectric effect, and pair production. Hainfeld II does not disclose or suggest the use of rhenium as an imaging contrast agent, and particularly does not disclose or suggest their use or suitability as a contrast agent for acoustic diagnosis or imaging (e.g., ultrasound sound waves). In that regard, it is noted that the paragraph in Hainfeld II which the Examiner cites as disclosing the use of rhenium in Hainfeld II's methods, also lists several other materials (e.g., Bismuth and Lead) which have low acoustic impedances below 35×10^5 g/cm^{2}s (e.g., Bismuth = 21.5×10^5 g/cm^{2}s; Lead = 24.6×10^5 g/cm^{2}s) and therefore are not suitable for the methods of diagnosis and imaging claimed in the present patent application.

Accordingly, Applicants respectfully submit that there is nothing in the cited art that suggests the methods of diagnosis and imaging of claims 30 and 31 that require administering solid rhenium nano-particles having an acoustic impedance above

35.10^5 g/cm^{2}s, and receiving ultrasound sound wave reflections from these solid rhenium nano-particles.

Therefore, for at least these reasons, Applicants respectfully submit that claims 30 and 31 are patentable over the cited art. Accordingly, Applicants respectfully request that the rejections of claims 30 and 31 be withdrawn.

For all of the foregoing reasons, Applicants respectfully submit that the rejections of claims 15-33 are all in error. Therefore, Applicants respectfully request that that the Board reverse the rejections of claims 15-33, and the application be returned to the Examiner for further processing.

Respectfully submitted,

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